

**SYNTHESES AND CHIROPTICAL PROPERTIES
OF SOME 3-SUBSTITUTED THIOPHENES**

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OF SOME 3-SUBSTITUTED THIOPHENES

av

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Aspects of the Preparation of Cyclohexenyl- and menthenylthioenynes
via Ring-Opening of Thiophenes

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Abstract

Aspects of the preparation of cyclohexenyl- and menthenylthioenynes via ring-opening of thiophenes. Svensson, A.; Karlsson, J.O.; Hallberg, A. (Division of Organic Chemistry 1, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden).

Treatment of 2,5-dimethyl-3-(1-menthenyl)-4-bromothiophene (IIIa) and 2,5-dimethyl-3-(1-cyclohexenyl)-4-bromothiophene (IIIb) with butyllithium gave the thiodienynes Va and Vb, respectively, via ring-opening of the corresponding 3-lithio derivatives.

2,5-Dimethyl-3-(1-menthenyl)-4-bromothiophene-1,1-dioxide (IV) gave the sulfone VI under similar conditions. UV spectra of IIIa-b, IV, Va-b and some related compounds have been recorded and compared. The rotational barrier of compound VI was determined.



Introduction

The organolithium-induced ring-opening of thiophenes, leading to compounds with thioenyn fragment I with cis geometry around the double bond, has recently been studied extensively in our laboratories [1,2]. The stability of the intermediate 3-lithium derivative, which undergoes an E1cB type elimination, has been found to be quite dependent on the substitution pattern of the thiophene ring, and the effects of several different substituents have been examined [1,3-6]. In order to evaluate the utility of this ring-opening reaction for the synthesis of compounds with the cross-conjugated thiodienyn fragment II, we have now carried out an investigation starting with two thiophene derivatives, each substituted with a vinyl function, a functionality whose effects on the reaction had not previously been studied. The easily available 2,5-dimethyl-3-(1-menthenyl)-4-bromothiophene (IIIa) and 2,5-dimethyl-3-(1-cyclohexenyl)-4-bromothiophene (IIIb) which were used as precursors in a ongoing study of the chiroptical properties of bicyclic systems, were chosen as starting materials.

Secondly, we wish to report results in connection with our recent finding that the reaction between different substituted 3-halothiophene-1,1-dioxides and organolithium reagents affords products resulting from two different ring-opening sequences [7]. We regarded 2,5-dimethyl-3-(1-menthenyl)-4-bromothiophene-1,1-dioxide (IV), with its bulky β -menthenyl substituent, as an interesting substrate.

Results and Discussion

Treatment of IIIa and IIIb with 1 eq. of butyllithium at room temperature in ether for one hour, and subsequent alkylation with excess butyl bromide, gave (E)-2-butylthio-3-(1-menthenyl)-2-hexen-4-yne (Va) and (Z)-2-butylthio-3-(1-cyclohexenyl)-2-hexen-4-yne (Va) in yields of 62 % and 44 %, respectively. Apparently it is possible to utilize these vinyl thiophenes in the ring-opening reaction for the specific preparation of compounds with the structural element II, in a convenient way.

The UV spectra of the products were found to be similar, with a $\lambda_{\max}$ at 280 nm. In the parent system XI, without the cyclohexenyl group present, the $\lambda_{\max}$ of the enyne chromophore appears at 5 nm shorter wavelength (Fig. 1). These results, and observations in connection with the ring-opening of IV (vide infra) prompted us to record and compare the UV spectra of the starting materials IIa and IIb, a compound with intermediate bulkiness around the pivot bond, 2,5-dimethyl-3-(2-methyl-1-cyclohexenyl)-4-bromothiophene (IIIc) and the derivatives 3-(1-menthenyl)thiophene (IIId) and 3-(1-cyclohexenyl)thiophene (IIIe) without 2,4- and 5-substituents present on the thiophene nucleus (Fig. 2). All five compounds showed $\lambda_{\max}$ in the region 240-245 nm. The monosubstituted thiophenes IIId and IIIe gave somewhat broader absorption in this region. The least substituted derivative, 3-(1-cyclohexenyl)thiophene (IIIe), where we expected no steric hindrance to coplanarity,

gave a λ_{max} at 222 nm. The corresponding absorption in the UV spectra of the other monosubstituted thiophene derivative IIId seems to appear at shorter wavelength, 210 nm. The weak shoulder in the spectrum of the tetrasubstituted thiophene, with no alkyl substituents in the cyclohexene moiety II Ib, indicates that the same band has been shifted further toward shorter wavelength. A tendency toward a shoulder around 210 nm can be seen in the spectrum of II Ic. No corresponding absorption appears in the spectrum of IIIa, where the bulkiness around the pivot bond is optimized. We assume this absorption to be due to conjugation between the double bond and the aromatic part of the molecule, and thus more steric hindrance to coplanarity, resulting in removal of conjugation, gives rise to a hypsochromic effect. Similar observations have been reported concerning other 3-menthene-substituted thiophenes [8], phenylcyclohexenes [9] and naphthylcyclohexenes [10].

CD and UV spectra of the optically active menthene derivatives IIIa, Va, IV and VI are shown in Figs. 3 and 4. All of them exhibit Cotton effects around 200 and 250 nm. The data are summarized in Table I.

The reaction of the dioxide IV with butyllithium at -70°C in ether gave, after quenching the reaction mixture with methyl iodide in dimethyl sulfoxide, 3-(1-menthenyl)-2-methylsulfonyl-2-hexen-4-yne (VI) in 34 % yield, and also a 63 % yield (GLC) of butyl bromide. According to GLC/MS analysis, the crude material after work-up consisted of several by-products, none of which corresponded to the expected VII. Furthermore, compound VII could not be traced in

in the reaction mixture before treatment with methyl iodide. GLC signals from compounds in lower yield than ca. 2 % of the total amount passing the column were not analyzed. This result was of interest, considering our earlier findings concerning ring-opening of thiophene-1,1-dioxides [7]. We established that 2,5-dialkyl-3-halothiophene-1,1-dioxides ring-open either via a) an organolithium attack on the 5-carbon or b) via a halogen-metal exchange reaction, as outlined in Scheme 2. The formation of the isomeric vinylacetylenes is interesting from a preparative point of view and it is possible to get a high isomer ratio by changing 5-substitutents. This reaction is favoured when the halogen exhibits little tendency to undergo halogen-metal exchange. Thus, bromo derivatives afforded products from both reaction sequences, while chloro derivatives gave exclusively products as a result from an initial nucleophilic attack. The possibility that a one electron transfer reaction is involved in the mechanisms cannot be excluded, but will not be discussed here. Based on earlier indications [8] that the bromo atom of IIIc undergoes halogen-metal exchange very slowly, we argued that the corresponding dioxide IV could be expected to give products resulting from an initial organolithium attack on the 5-carbon. However, formation of VI, and the high yield of butyl bromide, show that halogen-metal exchange had occurred predominantly. Although the reason for the dominant halogen-metal exchange is not obvious, steric factors due to non-coplanarity between the rings as suggested by the UV spectrum of the corresponding thiophene IIIa and by Dreiding molecular models, might be invoked. Electronic effects of the exocyclic double bond

favouring halogen-metal exchange can however not be excluded. As a comparison, 3-bromo-5-tert.-butyl-2-methylthiophene-1,1-dioxide under the same conditions gives a low yield (5.5 %) of products derived from butyllithium attack on the 5-carbon [11].

The ^1H NMR spectra of Va and VI both exhibited a doublet and a singlet around 2 ppm. We expected the signals from the propargylic and vinylic methyl groups to appear as singlets in this region as in the spectrum of the cyclohexene derivative Vb. To establish the origin of the doublets, whether long-range coupling or hindered rotation were involved, we recorded the spectrum of VI on a 360 MHz NMR spectrometer. From this it became clear that the splitting was due to hindered rotation, since the splitting is field dependent. Furthermore a "doubling" of the entire spectrum could be seen at room temperature at the higher frequency. We found the coalescence of the doublet to occur at 59°C in o-dichlorobenzene at 100 MHz, corresponding to a rotational barrier of $18.4 \pm 0.3 \text{ kcal/mol}$ ($\Delta\nu = 2.4 \text{ Hz}$). In o-dichlorobenzene the singlet at 2.07 ppm (CDCl_3) moved upfield, whereas the doublet did not move to any great extent. This indicates the singlet to originate from the propargylic methyl group, since this should be better solvated and more shielded by the aromatic solvent than the vinylic one close to the electro-negative sulfonyl moiety. Also our results clearly show the menthenyl substituent to be out of the enyne plane, which we also believe is the case for the other menthenyl derivative Va.

Applying reported methods [8,12,13] for the preparation of IIIa and IIIc-e to the synthesis of IIb gave the [c]-annelated thiophene derivative VIII as a by-product. A smaller amount of 2,5-dimethyl-

-3,4-dibromothiophene also remained. The yield of VIII was lower when the halogen-metal exchange was performed in dilute solution. We preferred to prepare IIb via isolation of the initially formed lithium alcoholate of the alcohol IX. Treatment of IX with p-toluene-sulfonic acid in toluene gave IIb in 23 % yield.

After oxidation of IIIa with m-chloroperbenzoic acid, 2,5-dimethyl-3-(1-menthenyl)-4-bromothiophene-1,1-dioxide (IV) was obtained. When the cyclohexene derivative IIb was subjected to the same reaction conditions, a ring contraction occurred instead, probably via epoxidation [14], resulting in the formation of 2,5-dimethyl-3-(1-formylcyclopentenyl)-4-bromothiophene (X) as the main product.

Experimental

All metalations were performed in dry solvents under nitrogen, using septum technique. ^1H NMR spectra were recorded on a Jeol MH 100 and a Nicolet 360 WB spectrometer equipped with a ^1H probe. The UV spectra were recorded on a Cary 16 spectrophotometer and the IR spectra were recorded on a Perkin-Elmer 298 spectrometer. Mass spectra were obtained using a Finnigan 4021 (Data System Incos 2100) gas chromatography-mass spectrometer and were in accordance with the proposed structures. Gas chromatograms were recorded on a Varian 3700 equipped with a OV 101, 3 %, 2.5 m, Varaport 30,80/100 mesh and F.I.D. The GLC yields were determined by comparison of the increase of the GLC peak integrals upon addition of known amounts of authentic material. Compounds IIa [8], IIc [12], IIId [8] and IIIE [13] were available in our laboratories.

2,5-Dimethyl-3-(1-cyclohexenyl)-4-bromothiophene (IIb).

To a solution of 11.2 g (40 mmol) of 3,4-dibromo-2,5-dimethylthiophene in 150 ml of dry ether, 26.8 ml (40 mmol) of 1.5 N butyllithium in hexane was added at -70°C . After 30 minutes, 3.92 g (40 mmol) of cyclohexanone in 5 ml of ether was added to the reaction mixture, and after another 10 minutes the cooling bath was removed and the stirring stopped. The solvent was decanted and the precipitate was carefully washed with ether and was then hydrolysed with water. The organic material was taken up in the ether, and after drying and evaporation it was dissolved in toluene

and refluxed with 1.0 g of *p*-toluenesulfonic acid for 30 minutes. The organic phase was washed with water and aqueous sodium hydrogen carbonate, dried (magnesium sulfate) and evaporated to give 2.45 g (23 %) of the title compound (IIIb) as an oil after chromatography (silica/hexane).

NMR (CDCl_3): δ 5.56 (bt, 1H, vinylic), 2.32 (s, 6H, CH_3), 2.16-1.70 (m, 8H, CH_2). [Found: C 52.8; H 5.50; S 12.1. Calc. for $\text{C}_{12}\text{H}_{15}\text{BrS}$ (271.2): C 53.1; H 5.57; S 11.8.]

In one run the total reaction mixture was subjected to the elimination procedure described. A GLC/MS analysis was performed before chromatography, showing that 3 % of the starting material remained and that compound VIII had been formed in 6 % yield. Performing the halogen-metal exchange in a more concentrated solution resulted in 6 % of the starting material and formation of dispiro[cyclohexane-1,1',4',6'-dimethylthieno[3,4-c]furan-3',1''-cyclohexane] (VIII) in 19 % isolated yield. It crystallized from the crude product upon standing and was recrystallized from hexane. M.p. 157-158°C. NMR (CCl_4): δ 2.22 (s, 6H, CH_3), 1.65 (m, 20H, CH_2). [Found: C 74.4; H 9.02; S 11.0. Calc. for $\text{C}_{18}\text{H}_{26}\text{OS}$ (290.5): C 74.4; H 9.02; S 11.0.]

(+)-2,5-Dimethyl-3-(1-menthenyl)-4-bromothiophene-1,1-dioxide (IV).

To a solution of 326 mg (1.00 mmol) of 2,5-dimethyl-3-menthenyl-4-bromothiophene IIIa in 25 ml of methylene chloride at 5°C, 382 mg (2.00 mmol) of *m*-chloroperbenzoic acid was added. After 4 days the reaction mixture was filtered and the filtrate was then extracted several times with an aqueous sodium carbonate solution. After evaporation of the dried (magnesium sulfate) methylene chloride

phase, the crystalline residue was recrystallized from hexane to give 240 mg, 67 %, of the title compound IV.

$[\alpha]_D^{25} = +45.6^{\circ}$ ($c = 0.50$, ethanol). IR: 1300, 1180 cm^{-1} (SO_2).

NMR (CDCl_3): δ 2.10 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.04-0.86 (m, 9H, $\text{CH}(\text{CH}_3)_2$ and $\text{CH}-\text{CH}_3$, $J_{\text{CH},\text{CH}_3} = 6.8$ Hz).

[Found: C 52.7; H 6.34; S 9.01. Calc. for $\text{C}_{16}\text{H}_{23}\text{BrSO}_2$ (359.3): C 53.5; H 6.45; S 8.92.]

2,5-Dimethyl-3-(1-formylcyclopentyl)-4-bromothiophene (X).

A solution of 277 mg (1.00 mmol) of 2,5-dimethyl-3-(1-cyclohexene)-4-bromothiophene IIb in 25 ml of methylene chloride was prepared and 191 mg (1.00 mmol) of *m*-chloroperbenzoic acid was added at 5°C . After reaction for 4 days and the same work-up procedure as for the preparation of IV, 114 mg (40 %) of 2,5-dimethyl-3-(1-formylcyclopentyl)-4-bromothiophene (X) was obtained as an oil after chromatography (silica, hexane/ethyl acetate, 90/10). The compound decomposed on standing.

IR: 1720 cm^{-1} ($\text{C}=\text{O}$). NMR (CDCl_3): δ 9.36 (s, 1H, CHO), 2.47 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.75-1.50 (m, 8H, CH_2).

Ring-opening Reactions

(E)-(+)-2-Butylthio-3-(1-menthenyl)-2-hexen-4-yne (Va) and (Z)-2-butylthio-3-(1-cyclohexenyl)-2-hexen-4-yne (Vb). To a stirred solution of 3.5 mmol of 2,5-dimethyl-3-(1-menthenyl)-4-bromothiophene IIIa and of 2,5-dimethyl-3-(1-cyclohexenyl)-4-bromothiophene IIIB, respectively, in 20 ml of ether, 2.6 ml (3.9 mmol) of 1.5 N butyllithium in hexane was added dropwise at room temperature. After one hour, excess butyl bromide (14 mmol) was added and the stirring was continued over night. The reaction mixture was poured into water and the aqueous phase was extracted several times with ether. The combined organic phases were washed with water, dried (magnesium sulfate) and evaporated to give oils. Chromatography (silica, hexane/ethyl acetate, 95/5) was used for isolation of the title compounds.

(E)-(+)-2-Butylthio-3-(1-menthenyl)-2-hexen-4-yne (Va):

0.58 g (62 %). $[\alpha]_D^{25} = +60.3^0$ ($c = 0.74$, ethanol). IR: 2205 cm^{-1} ($\text{C}\equiv\text{C}$).

NMR (CDCl_3): δ 2.75 (t, 2H, SCH_2), 1.1-2.5 (m, 8H, aliphatic), 2.02 (s, 3H, propargylic or vinylic CH_3), 1.90 (d, 3H, vinylic or propargylic CH_3), 0.80-1.00 (m, 12H, aliphatic CH_3). $J_{\text{SCH}_2, \text{CH}_2} = 7.0\text{ Hz}$, $J_{\text{CH}, \text{CH}_3} = 6.8\text{ Hz}$, $J_{\text{CH}_2, \text{CH}_3} = 7.0\text{ Hz}$.

[Found: C 78.2; H 10.3; S 11.0. Calc. for $\text{C}_{20}\text{H}_{32}\text{S}$ (304.5):

C 78.8; H 10.6; S 10.5.]

(Z)-2-Butylthio-3-(1-cyclohexenyl)-2-hexen-4-yne (Vb):

0.40 g (44 %). IR: 2205 cm^{-1} ($\text{C}\equiv\text{C}$). NMR (CDCl_3): δ 5.68 (m, 1H, vinylic), 2.76 (m, 2H, SCH_2), 2.0-2.3 (m, 4H, allylic), 2.04 (s, 3H,

propargylic or vinylic CH_3), 2.01 (s, 3H, propargylic or vinylic CH_3), 1.3-1.8 (m, 8H, aliphatic), 0.97 (t, 3H, butyl- CH_3).

$J_{\text{CH}_3, \text{CH}_2} = 7.0 \text{ Hz}$.

[Found: C 77.2; H 9.35; S 13.0. Calc. for $\text{C}_{16}\text{H}_{24}\text{S}$ (248.4):

C 77.4; H 9.74; S 12.9.]

(Z)-2-Butylthio-2-hexen-4-yne (XI) was prepared in the same way as Va and Vb from 23 g (0.10 mmol) of 2,5-dimethyl-3-iodothiophene [15] in 200 ml of dry ether, 73 ml (0.11 mmol) of 1.5 N butyllithium and 70 g (0.40 mmol) of butyl bromide. Yield: 9.2 g (55 %), b.p.₁₀ 107-115°C. IR; 2230 cm^{-1} (C-C).

NMR (CDCl_3): δ 5.36 (m, 1H, 3-H), 2.82 (t, 2H, SCH_2), 2.04 (m, 3H, 6- CH_3), 1.99 (bs, 3H, 1- CH_3), 1.1-1.7 (m, 4H, aliphatic), 0.90 (t, 3H, CH_2CH_3). $J_{3\text{-H}, 6\text{-CH}_3} 1.5 \text{ Hz}$, $J_{\text{CH}_2, \text{CH}_3} 6.5 \text{ Hz}$.

[Found: C 70.9; H 9.16. Calc. for $\text{C}_{10}\text{H}_{16}\text{S}$ (168.3): C 71.4; H 9.58.]

(E)-(+)-3-(1-Menthenyl)-2-methylsulfonyl-2-hexen-4-yne (VI).

To a solution of 0.40 g (1.2 mmol) of 2,5-dimethyl-3-(1-menthenyl)-4-bromothiophene-1,1-dioxide (IV) in 20 ml of ether, 1.8 ml (2.7 mmol) of 1.5 N butyllithium in hexane was added at -70°C.

After reaction for one hour, a sample of the reaction mixture was hydrolysed and analysed on GLC/MS. The main part of the reaction mixture was evaporated and 10 ml of dimethyl sulfoxide was added followed by excess of methyl iodide (10 mmol). After stirring over night at room temperature, a sample for GLC/MS analysis was again removed, and the main part of the reaction mixture was poured into ether/water. The aqueous layer was extracted and the combined organic phases were washed, dried (magnesium sulfate) and evaporated.

After chromatography (silica, hexane/ethyl acetate, 80/20) 0.11 g (31 %) of (E)-(+)-3-(1-menthenyl)-2-methylsulfonyl-2-hexen-4-yne (VI) was isolated as an oil.

$[\alpha]_D^{25} = +12.8^0$ ($c = 0.078$, ethanol). IR: 2205 cm^{-1} ($\text{C}\equiv\text{C}$).

NMR (CDCl_3): δ 3.01 (s, 3H, CH_3SO_2), 1.0-2.8 (m, 8H, aliphatic), 2.07 (s, 3H, propargylic), 2.02 (d, 3H, vinylic CH_3), 0.85-1.03 (m, 9H, $-\text{CH}(\text{CH}_3)_2$ and $-\text{CH}-\text{CH}_3$). $J_{\text{CH},\text{CH}_3} = 6.8\text{ Hz}$.

[Found: C 69.9; H 8.32; S 11.3. Calc. for $\text{C}_{17}\text{H}_{26}\text{SO}_2$ (294.5): C 69.8; H 8.90; S 10.9.]

The coalescence experiments were carried out in *o*-dichlorobenzene on a Jeol MH 100 MHz NMR spectrometer. The coalescence of the doublet at 2.02 ppm occurred at 59^0C . At 100^0C a coupling of 0.7 Hz between the propargylic and vinylic methyl groups appeared clearly.

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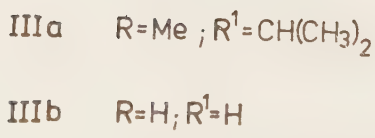
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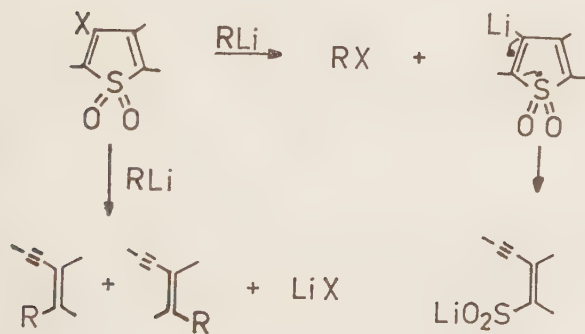
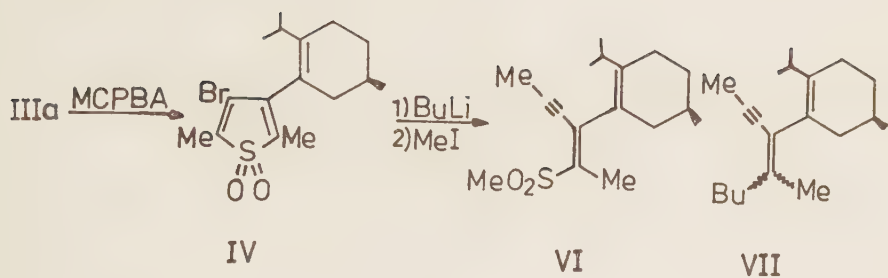
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Table I. CD and UV values

Compound ^a	$\lambda_{\max}$ (nm) and ϵ ($M^{-1}cm^{-1}$)	$\lambda_{\max}$ (nm) and $[\theta]_{\max}$ ($deg.mol^{-1}cm^2$)	
IIIa	193 (24400)	244 (7400)	
IV	220 (6000)	300 (4600)	
Va		280 (9600)	
VIa	190 (12600)	247 (10000)	
IIIb	190 (18800)	241 (7400)	
IIIc	193 (28000)	241 (7400)	
IIId	207 (12400)	240 (5800)	
IIIe	221 (8800)	240 (8200)	244 (8000)
Vb	215 (7000)	280 (8400)	
XI	210 (5000)	275 (11600)	

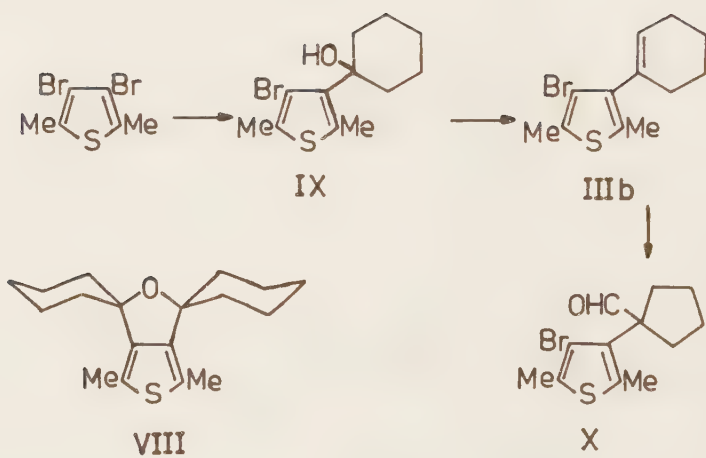
^a Solvent: acetonitrile.





$\text{X} = \text{Br, Cl}$
 $\text{R} = \text{Alkyl, phenyl}$

Scheme 2



Scheme 3

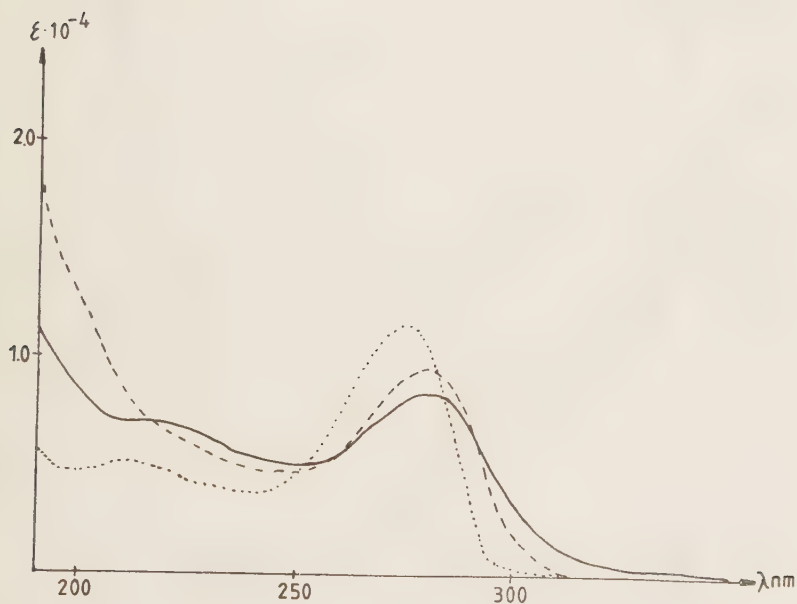
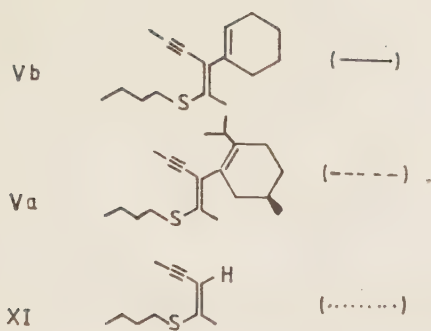


Fig. 1. UV spectra of 2-butylthio-3-(1-menthenyl)-2-hexen-4-yne (Va),
 2-butylthio-3-(1-cyclohexenyl)-2-hexen-4-yne (Vb) and
 2-butylthio-2-hexen-4-yne (XI) in acetonitrile.

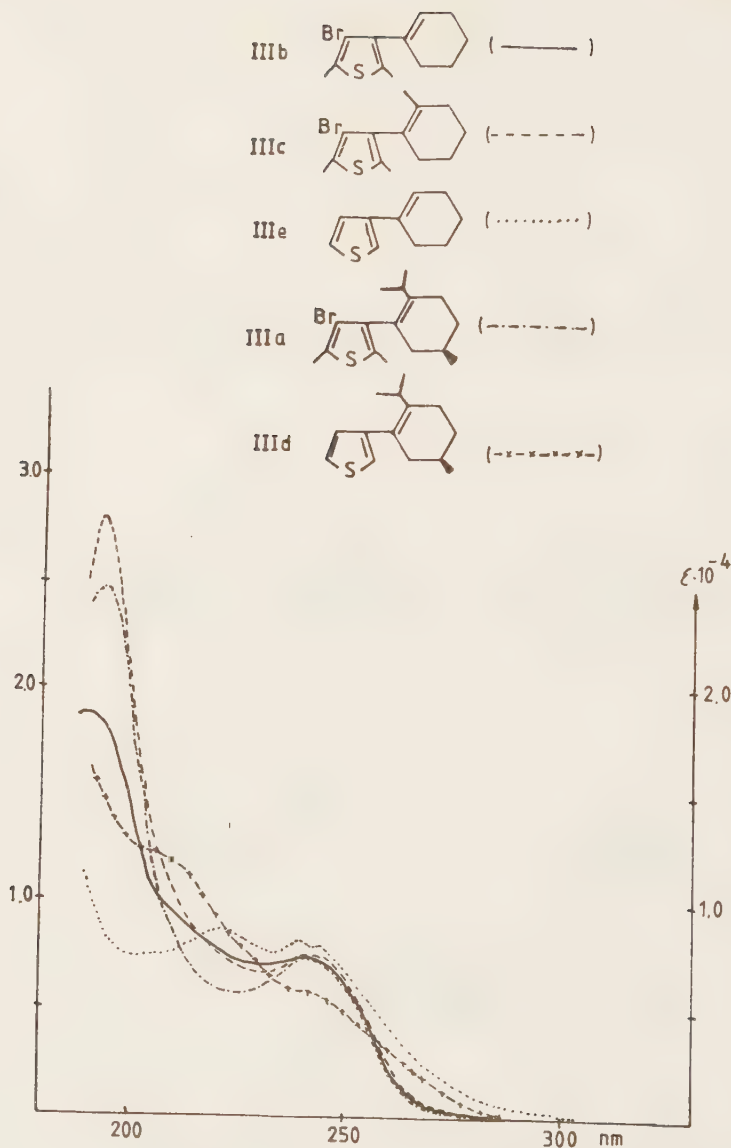


Fig. 2. UV spectra of 2,5-dimethyl-3-(1-menthenyl)-4-bromothiophene (IIIa), 2,5-dimethyl-3-(1-cyclohexenyl)-4-bromothiophene (IIIb), 2,5-dimethyl-3-(2-methyl-1-cyclohexenyl)-4-bromothiophene (IIIc), 3-(1-menthenyl)thiophene (IIId) and 3-(1-cyclohexenyl)thiophene (IIIe) in acetonitrile.

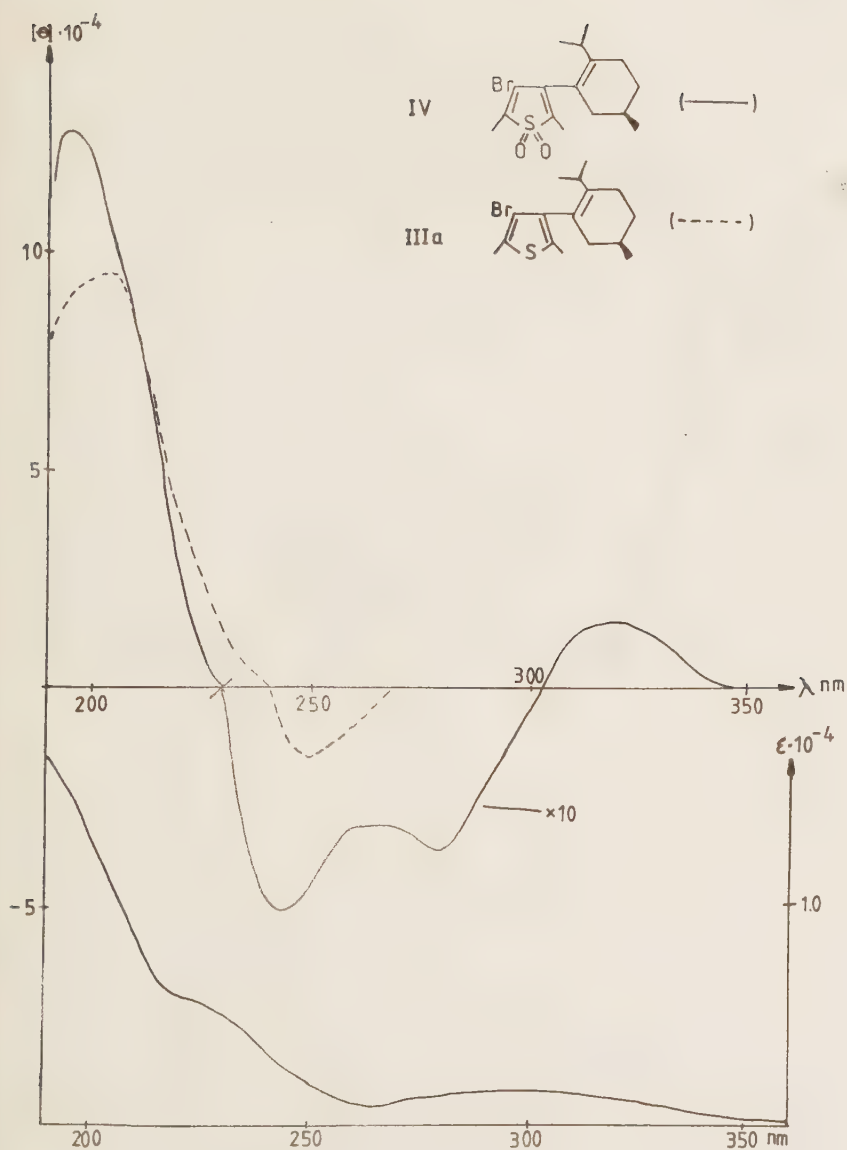


Fig. 3. CD and UV of 2,5-dimethyl-3-(1-menthenyl)-4-bromothiophene-1,1-dioxide (IV) and 2,5-dimethyl-3-(1-menthenyl)-4-bromothiophene (IIIa) in acetonitrile.

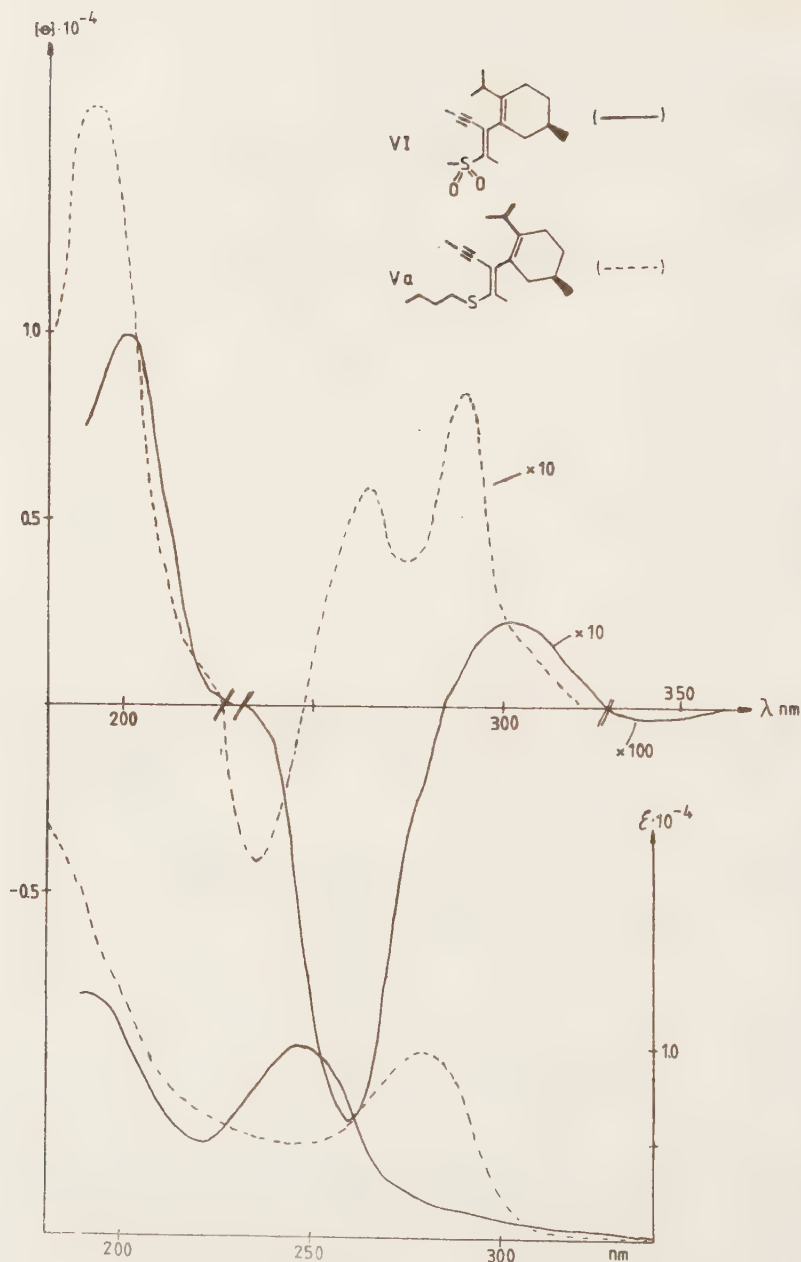


Fig. 4. CD and UV of 2-butylthio-3-(1-menthenyl)-2-hexen-4-yne (Va) and 3-(1-menthenyl)-2-methylsulfonyl-2-hexen-4-yne (VI) in acetonitrile.

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Abstract The syntheses of <u>4,4'-dicarboxy-2,2'-diformyl-3,3'-bithienyl</u>, <u>2,2',4,4'-tetracarboxy-3,3'-bithienyl</u>, <u>2,5-dimethyl-3-(2-methyl-1-cyclohexenyl)-4-thiophenecarboxylic acid</u> and some related compounds, <u>(-)-menthene substituted thiophenes</u>, <u>2,5-dimethyl-3-(2,2,6-trimethyl-6-cyclohexenyl)-4-thiophenecarboxylic acid</u> and some related compounds and <u>α-methoxy-3-thienylacetic acids</u> are discussed. Some <u>cross-conjugated thiodienynes</u> were prepared by <u>ring-opening reactions</u>. <u>Resolutions</u> were made with cinchonidine and brucine. The <u>absolute configurations</u> of the bithienyls were deduced by chemical methods. The <u>Circular Dichroism (CD)</u> and <u>UV spectra</u> are discussed. A comparison of the CD spectra of bithienyls, cyclohexenylthiophenes and <u>α-methoxy-3-thienylacetic acids</u> are made showing great similarities.		
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Signature Arne Svensson

Date April 15, 1982.

This review summarizes results from the following papers, which will be referred to as (1)...(6).

1. Håkansson, R. and Svensson, A.
Stereochemistry of 3,3'-Bithienyls. XVIII.
Syntheses, absolute configurations and circular dichroism spectra of 4,4'-dicarboxy-2,2'-diformyl-3,3'-bithienyl and 2,2',4,4'-tetracarboxy-3,3'-bithienyl.
Chemica Scripta 1975, 7, 186.
2. Svensson, A. and Håkansson, R.
Preparation of 2,5-dimethyl-3-(2-methyl-1-cyclohexenyl)-4-thiophenecarboxylic acid and 2,5-dimethyl-3-(2-methyl-2,6-cyclohexadienyl)-4-thiophenecarboxylic acid.
Chemica Scripta 1981, 18, 202.
3. Svensson, A. and Håkansson, R.
Preparation, resolution and CD spectra of 2,5-dimethyl-3-(2,2,6-trimethyl-6-cyclohexenyl)-4-thiophenecarboxylic acid and some related compounds.
Chemica Scripta, in press.
4. Svensson, A. and Håkansson, R.
Preparation and CD spectra of 2,5-dimethyl-3-(1-menthene)-4-thiophenecarboxylic acid and some related compounds.
Chemica Scripta, in press.
5. Svensson, A. and Håkansson, R.
Preparation, resolution and CD spectra of some α -methoxy-3-thienylacetic acids.
Chemica Scripta, in press.
6. Svensson, A., Karlsson, J.O. and Hallberg, A.
Aspects of the preparation of cyclohexenyl- and menthenyl-thioenynes via ring-opening of thiophenes.
Manuscript.

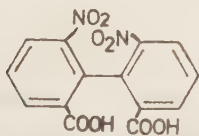
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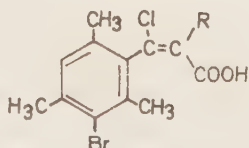
1. INTRODUCTION

The discovery and history of the optical isomerism of biphenyls, also called atropisomerism, are reviewed in several papers.¹⁻¹²

In 1907 Kaufler¹³ tried to explain why benzidine has certain properties not normal for a bicyclic molecule with coplanar rings and proposed a folded structure for the molecule. When studying this problem, Christie and Kenner¹⁴ in 1922 successfully resolved the dinitrodiphenic acid I and proposed the now accepted structure.



I



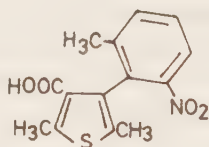
II

R=CH₃,H

Atropisomerism not only occurs in biphenyls, but it was also found in other biaromatic systems,^{2,3} or compounds where one aromatic ring is replaced by an olefin. This was shown by Adams et al who succeeded in resolving the arylolefins II in 1940.¹⁵⁻¹⁷ Meisenheimer¹⁸ showed, with measurements of atomic size, that the bulk of the ortho substituents was responsible for the hindered rotation and that it prevents a coplanar conformation. Other factors that influence the rotational barrier were investigated by Westheimer et al,⁴ Howlett¹⁹ and Pedersen.²⁰ Biaryls were investigated with optical methods by Mislow and coworkers,⁷⁻¹⁰ who also deduced the absolute configuration of a biphenyl by chemical methods. Later on it was confirmed with Bijvoet X-ray analyses.²¹⁻²⁴ This made it possible to deduce the configuration for many biphenyls. The Fredga quasi-racemate method was also used for the steric correlations.²⁵⁻²⁷

In the early 1960's Mislow et al used optical rotatory dispersion (ORD) for investigation of some biphenyls and binaphthyls and this was subsequently complemented by circular dichroism (CD) studies.⁹⁻¹²

The first example of atropisomerism involving a thiophene compound was demonstrated by Owen and Nord,²⁸ who resolved compound III in 1951.



III

The first atropisomeric bithienyl was resolved by Gronowitz and Frostling in 1961.²⁹ Since then, many optically active bithienyls have been made and their CD spectra investigated by Håkansson,³⁰ Wiklund³¹ and Almqvist.³²

One of the first optical active thiophenes was (-)-2-thienylglycolic acid made by Fujise in 1931.³³ Subsequently, the 3-isomer was made by Gronowitz.³⁴

The CD investigations of the compounds cited have revealed certain connections between the conformation and the CD spectrum. Biphenyls exhibit a Cotton effect at 240-250 nm, referred to as the conjugation band. The sign of this band can be related to the helicity of the biaryl skeleton. A cis-skew conformation of the (R)-biaryl results in a positive Cotton effect at 240-250 nm. Håkansson et al have found a comparable rule for 3,3'-bithienyls.³⁰ The CD spectra of a 3,3'-bithienyl of (R)-configuration reveals a negative band near or above 250 nm, followed by a positive band at shorter wavelengths.

In order to obtain more detailed information about the aromatic chromophore, and the thienyl chromophore in particular, we wished to investigate some chiral thiophene compounds in which the nearest ring is nonaromatic or has a chiral centre in the side chain. The aromatic transitions would then not be

coupled with other transitions. Comparison with the CD spectra of suitable bithienyls might give valuable information about the origins of the various bands.

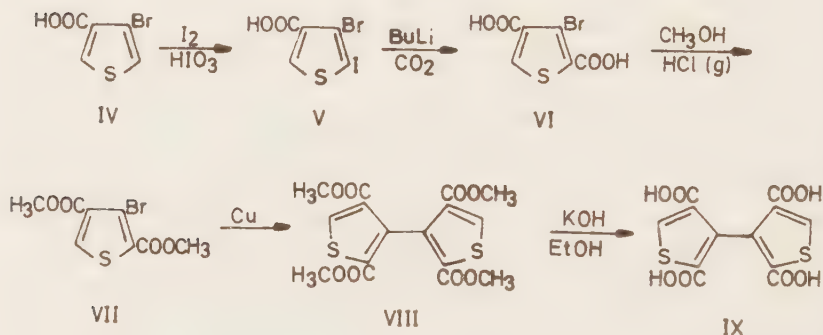
The present work was initiated by Professor Gronowitz and Docent Håkansson. It is the fourth part of an investigation of the chiroptical properties of substituted thiophenes.

2. SYNTHESSES OF 3-SUBSTITUTED THIOPHENES

2.1 Preparation of 4,4'-dicarboxy-2,2'-diformyl-3,3'-bithienyl and 2,2',4,4'-tetracarboxy-3,3'-bithienyl (Paper 1)

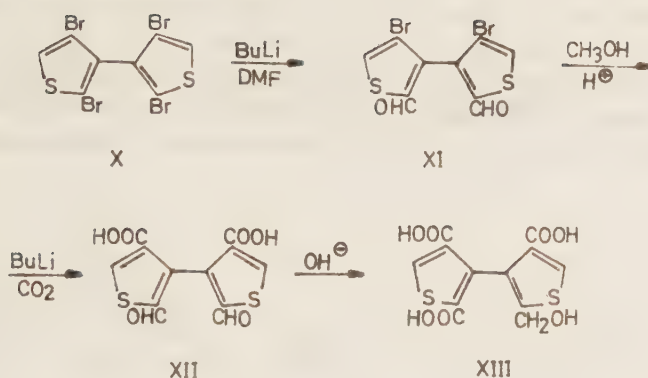
The preparations of the title compounds are outlined in Schemes 1 and 2.

Attempts to prepare IX by iodination of 2,2'-dicarboxy-3,3'-bithienyl result in a mixture of iodinated product.^{35,36} Instead, a modified Ullmann synthesis was used.



Scheme 1

Compound IV was iodinated with iodine-iodic acid, yielding V in 84 % yield. Via the lithium derivative of V, compound VI was obtained. Purification of the product was performed in the esterification step, as the by-products remained soluble in the solvent while VII crystallized. The bithienyl VIII was made from VII by reaction with copper powder in dimethylformamide. The yield seemed to depend on the quality of the copper powder used. Hydrolysis of VIII in alcoholic potassium hydroxide gave tetracarboxylic acid IX.



Scheme 2

Another synthetic path starts from 2,2',4,4'-tetrabromo-3,3'-bithienyl X. The dialdehyde XI is formed by reaction with butyllithium and dimethylformamide. By carbonating the 4,4'-dilithium derivative of the acetal, compound XII was obtained in 91 % yield. The tetracarboxylic acid IX could be obtained by oxidation with KMnO_4 , but the yield was low. The reaction was only used in connection with the determination of the absolute configuration.

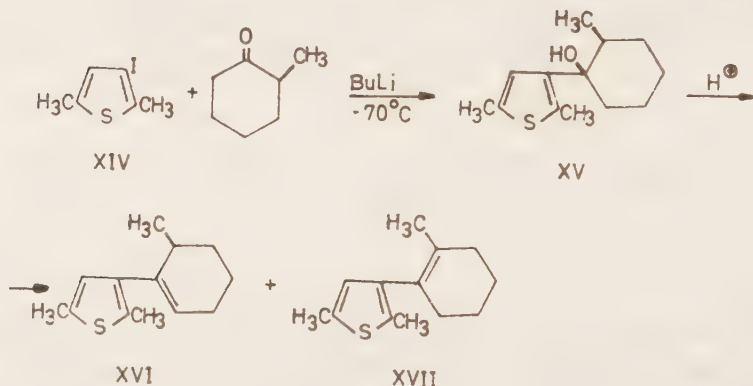
In connection with CD investigations of XII in 0.1 N sodium hydroxide it was found that a Cannizzaro reaction took place, yielding tricarboxylic acid XIII.

2.2 Preparation of 2,5-dimethyl-3-(2-methyl-1-cyclohexenyl)-4-thiophenecarboxylic acid and some related compounds (Paper 2)

A possible atropisomeric thienylcyclohexane molecule must have substituents in the positions ortho to the pivot bond in

both rings. However, a substituent in the cyclohexane ring induces a chiral centre. This is eliminated either by placing two substituents at the same carbon or introducing a double bond, e.g. by dehydration of an alcohol.

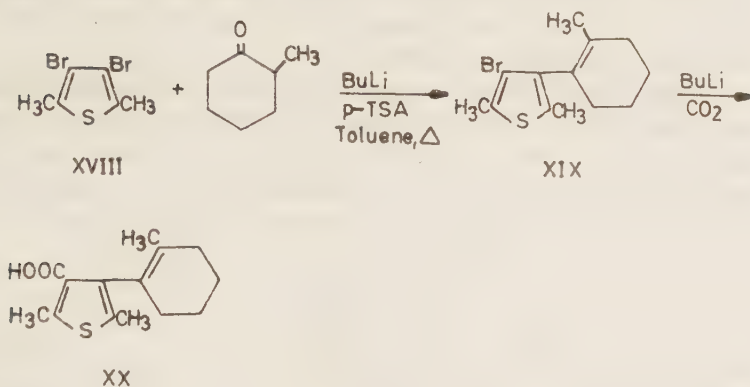
The dehydration of 1-phenylcyclohexanols was difficult to study before the introduction of NMR.^{39,40} Erroneous results were published that had to be corrected when investigated by NMR.⁴¹



Scheme 3

The dehydration reaction has been studied for 2,5-dimethyl-3-(2-methylcyclohexanol)-thiophene (XV), which was obtained from the lithium salt of XIV and 2-methylcyclohexanone (Scheme 3). The well known Saytzeff's rule predicts the double bond to be directed towards the most substituted carbon. However, the dehydration resulted in a mixture of compounds XVI and XVII which was difficult to separate. This was also found by Garbisch³⁷ and Rutherford et al³⁸ in the analogous phenyl system. An investigation was made with different dehydration reagents. The desired compound XVII was obtained by dehydration with p-toluenesulphonic acid in refluxing toluene, which indicates that the reaction is thermodynamically controlled.

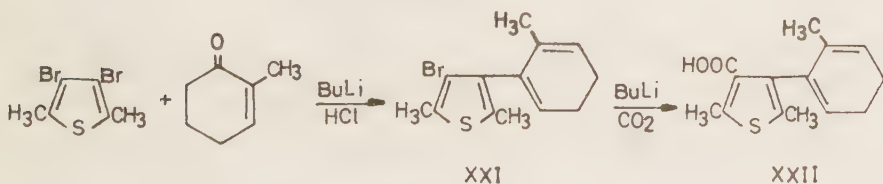
In Scheme 4 the synthesis of XX is presented.



Scheme 4

A carboxyl group is placed in the 4-position to induce atropisomerism and for resolution.

When the lithium salt of XVIII is reacted with 2-methyl-2-cyclohexenone, the position of the resulting double bond is unambiguous (Scheme 5) in the product XXI. Carboxylic acid XXII was prepared as outlined above.



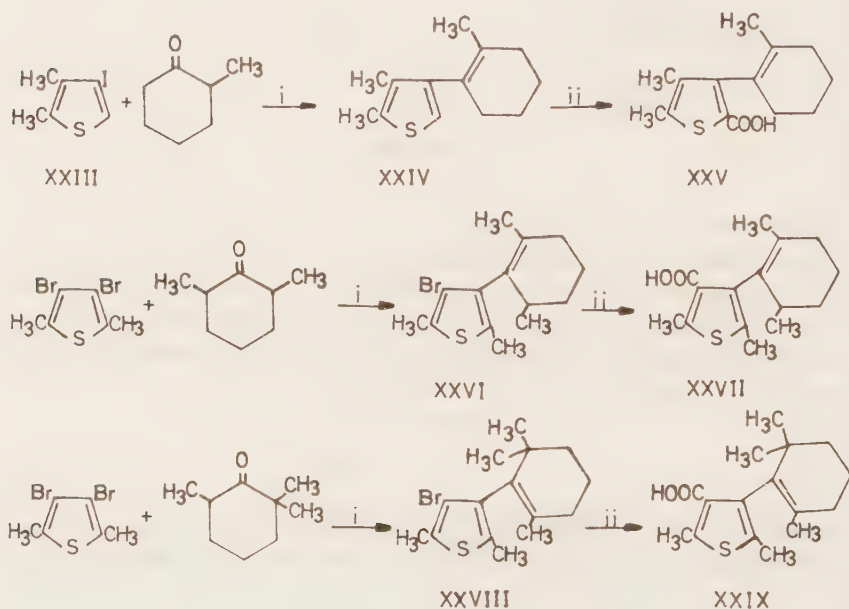
Scheme 5

2.3 Preparation of 2,5-dimethyl-3-(2,2,6-trimethyl-6-cyclohexenyl)-4-thiophenecarboxylic acid and some related compounds (Paper 3)

In Scheme 6 the syntheses of some presumptively atropisomeric cyclohexenyl thiophenes are depicted.

The lithium salt of XXIII was reacted with 2-methylcyclohexanone, yielding XXIV after dehydration with p-TSA. Carboxylic acid XXV was made by refluxing XXIV with butyllithium and subsequent carbonation.

Compound XXVI, with two methyl groups ortho to the pivot bond, was made from XVIII as previously described. Carboxylic acid XXVII, in addition to its possible atropisomerism, also has a chiral centre in the cyclohexene ring. The compound was however made from racemic 2,6-dimethyl-cyclohexanone.



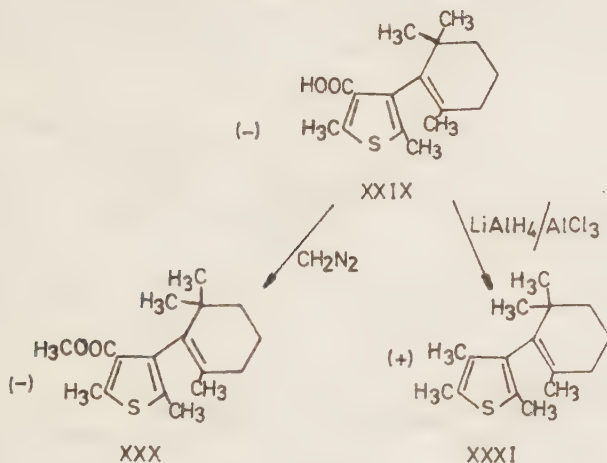
(i) BuLi ; p-TSA, Toluene, Δ
 (ii) BuLi ; CO₂

Scheme 6

The same synthetic path was used for compounds XXVIII and XXIX. It was necessary to raise the temperature to 0°C to get halogen-metal exchange in XXVIII. Reaction at -70°C gave only

starting material. Dreiding models reveal severe steric hindrance to rotation in compound XXIX, and it should be a racemic mixture of two atropisomeric forms.

In Scheme 7 optically active XXIX, obtained by resolution with brucine, the synthesis of methyl ester XXX, and the reduced derivative XXXI are shown.



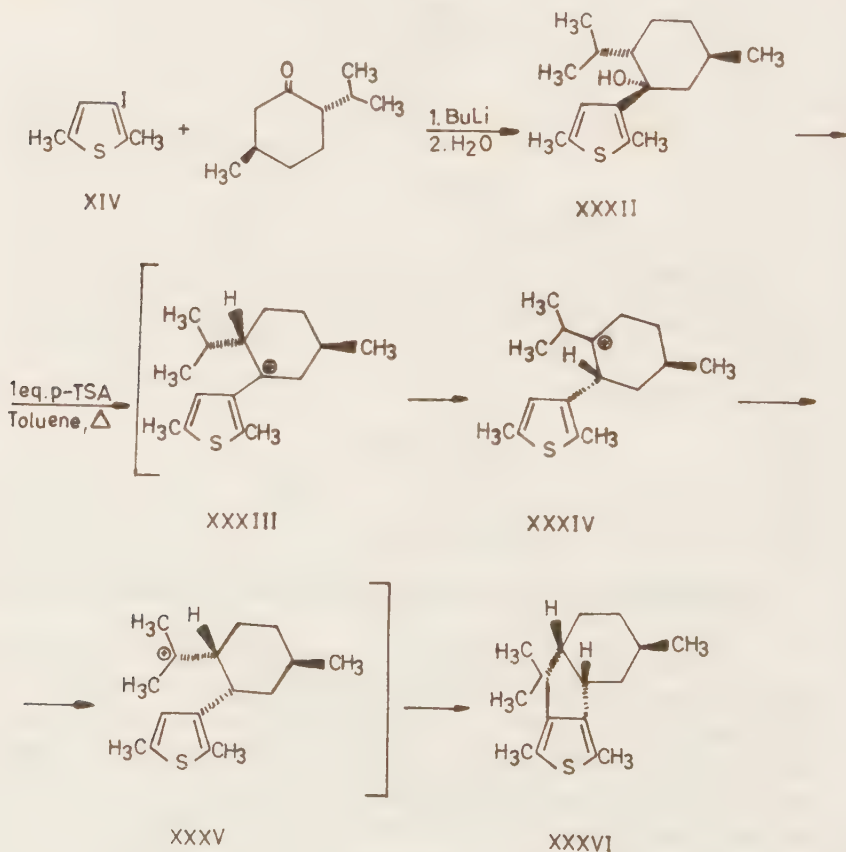
Scheme 7

2.4 Preparation of (-)-menthene substituted thiophenes (Paper 4)

The syntheses are outlined in Schemes 8-10. In each product there is one chiral centre with a definite configuration.

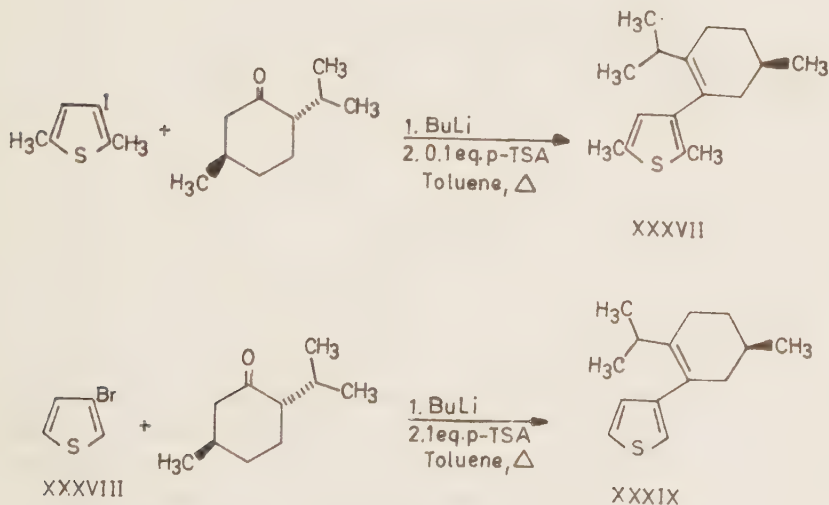
Metallation of XIV and subsequent reaction with (-)-menthone yielded the alcohol XXXII, which upon dehydration gave the unexpected compound XXXVI. Using molecular models this can be explained by assuming that the attack of thienyllithium takes place on the least hindered side of the menthone, forming the alcohol XXXII, where the thienyl and isopropyl groups are situated trans. The carbonium ion formed, XXXIII, is rearranged

via a 1,2-hydride shift to the 2-position in the cyclohexane ring, XXXIV, creating a chiral centre with (S)-configuration in the 1-position. Via another 1,2-hydride shift, the carbonium ion is rearranged to the isopropyl group, XXXV, creating a chiral centre in the 2-position with (R)-configuration. The isopropyl and thienyl groups are now in cis position in the cyclohexane ring and the distance between the 4-position in the thiophene and the isopropyl group is favourable for ring closure. The configurations at the three chiral centres in XXXVI would then be (1S, 2R, 5R).



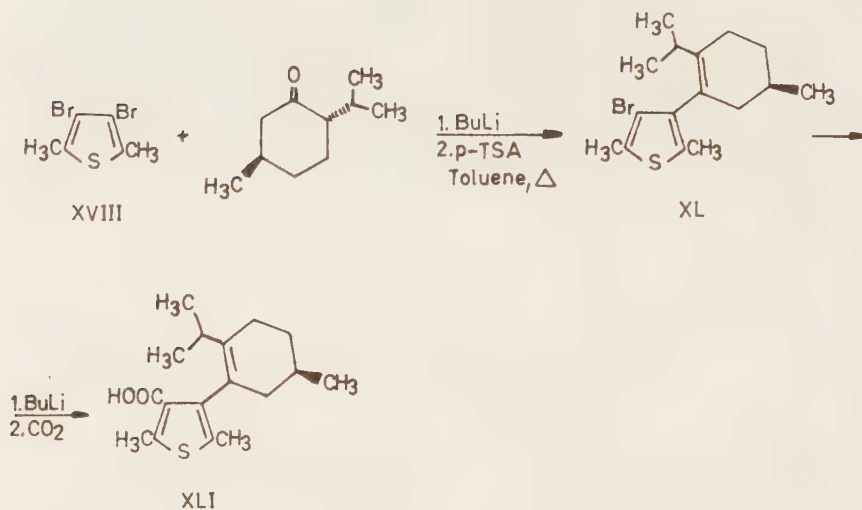
Scheme 8

Using a smaller amount of p-TSA gave the desired compound XXXVII (Scheme 9). Repeating the reaction starting from XXXVIII led exclusively to XXXIX and no ring closure was observed. This can be explained if the β -position of an unsubstituted thiophene is less nucleophilic than the corresponding position in XIV. The transition state in the formation of the 5-membered ring may also be favoured sterically by interaction of the 2-methyl group with the menthyl moiety. Formation of a ring on the c-side leads to less angle deformation than a ring closure to the b-side would do.⁴²



Scheme 9

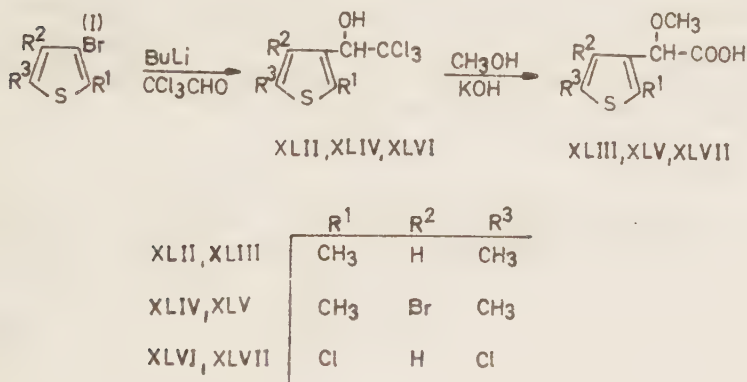
In Scheme 10 the preparation of carboxylic acid XLI is outlined.



Scheme 10

2.5 Preparation of some α -methoxy-3-thienylacetic acids (Paper 5)

In order to investigate the relation between the Cotton effects and the configuration at the asymmetric centre, the compounds in Scheme 11 were prepared.

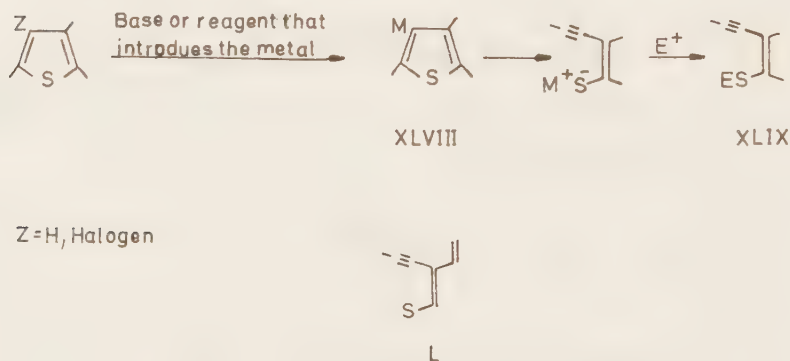


Scheme 11

The reaction starts from a 3-bromothiophene.⁴³ Halogen-metal exchange and subsequent reaction with chloral yields a trichloromethylcarbinol in approximately 70 % yield. This compound is reacted with potassium hydroxide in methanol. The resulting α -methoxy acid is obtained in rather low yield. The acid is isolated as its sodium salt whose solubility is increased by methyl groups or ortho-substituents.⁴⁴ This was however of minor importance as only a small amount is necessary for the chiroptical investigations.

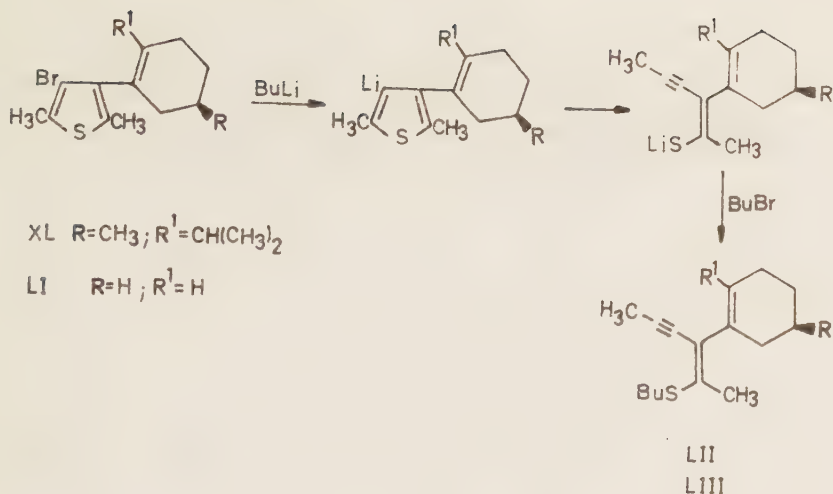
2.6 Preparation of some cyclohexenyl- and menthenyl-thioenynes

Organolithium induced ring-opening of thiophenes, leading to compounds with thioenyn fragment XLIX with *cis* geometry around the double bond (Scheme 12), has recently been studied extensively in our laboratories.^{45,46} The stability of the intermediate 3-lithium derivative, XLVIII, which undergoes an E_1CB type elimination, has been found to be very dependent on the substitution pattern of the thiophene ring, and effects of various substituents have been examined.^{45,47-50}



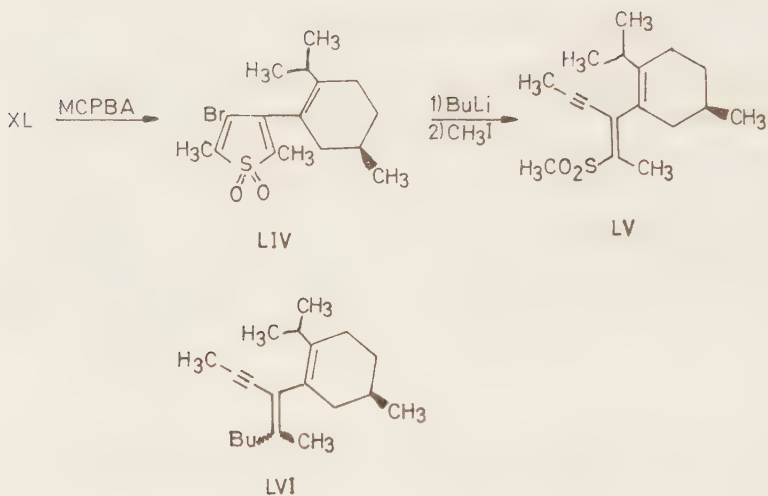
Scheme 12

Treatment of XL and LI with 1 eq. of butyllithium at room temperature in ether for one hour gave, after subsequent alkylation with excess butyl bromide, (E)-2-butylthio-3-(1-menthenyl)-2-hexen-4-yne (LII) and (Z)-2-butylthio-3-(1-cyclohexenyl)-2-hexen-4-yne (LIII) in 62 % and 44 %, respectively (Scheme 13). Apparently it is possible to utilize these vinylthiophenes in the ring-opening reaction for a specific preparation of compounds with the structural element L, in a convenient way.



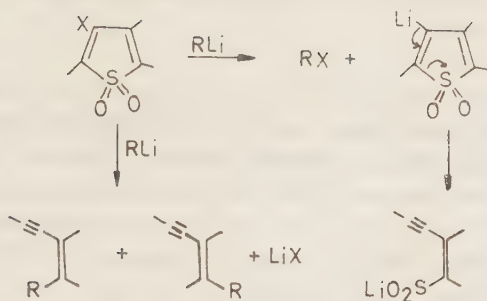
Scheme 13

The reaction of the dioxide LIV (Scheme 14) with butyllithium at -70°C in ether gave, after quenching the reaction mixture with methyl iodide in dimethyl sulphoxide, (E)-3-(1-menthenyl)-2-methylsulphonyl-2-hexen-4-yne (LV) in 34 % yield, and also a 63 % yield (GLC) of butyl bromide. According to GLC/MS analysis the crude material after work-up consisted of several by-products, none of which corresponded to the expected compound LVI. Nor could compound LVI be detected in the reaction mixture before treatment with methyl iodide.



Scheme 14

This result was interesting, considering earlier findings concerning ring-opening of thiophene-1,1-dioxides.⁵¹ It was established that 2,5-dialkyl-3-halothiophene-1,1-dioxides ring-open either via an organolithium attack on the 5-carbon or via a halogen-metal exchange reaction, as outlined in Scheme 15.



X=Cl, Br

R= Alkyl, Phenyl

Scheme 15

The formation of the isomeric vinylacetylenes is interesting from a preparative point of view, and it is possible by changing 5-substituents to get a high isomer ratio. This reaction is favoured when the halogen exhibits little tendency to undergo halogen-metal exchange. Thus, bromo derivatives afforded products from both reaction sequences, while chloro derivatives gave exclusively products as a result from an initial nucleophilic attack.

Based on earlier indications⁵² that the bromo atom of XL undergoes halogen-metal exchange very slowly, we argued that the corresponding dioxide LIV could be expected to give products resulting from an initial organo-lithium attack on the 5-carbon. However, formation of LV, and the high yield of butyl bromide shows that halogen-metal exchange had occurred predominantly. Although the reason for this is not obvious, steric factors due to noncoplanarity between the rings as suggested by the UV spectrum of the corresponding thiophene XL (see 5.3) and by Dreiding molecular models, might be invoked. Electronic effects of the exocyclic double bond favouring halogen-metal exchange can however not be excluded.

3. OPTICAL RESOLUTIONS AND ABSOLUTE CONFIGURATIONS (Papers 1,3,5)

Compounds IX, XII, XXIX, XLIII, XLV and XLVII were all resolved by salt formation with an optically active base such as brucine, cinchonidine or phenylethylamine. The active dialdehyde XII was obtained in part through a second-order asymmetric transformation, i.e. by salt formation with a suitable chiral base, all molecules of the acid may be transformed into one enantiomer due to a low barrier to configurational interconversion.

The absolute configurations of IX and XII were deduced by chemical methods. Dextrorotatory XII was reduced to (S)-(+)-2,2',4,4'-tetramethylbithienyl with known absolute configuration, and also oxidized to dextrorotatory tetracarboxylic acid IX. This implies that (+)-IX and (+)-XII have the (S)-configuration.

4. OPTICAL STABILITIES (Papers 1,3,6)

Compound XII was racemized in diglyme and compound IX in 0.1 N sodium hydroxide at three different temperatures. From the rate constants at different temperatures, the activation parameters were obtained from the Eyring equation:⁵³

$$\ln \frac{k}{T} = - \frac{\Delta H^\ddagger}{R} \frac{1}{T} + \frac{\Delta S^\ddagger}{R} + \ln \frac{Xk_b}{h}$$

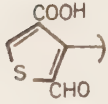
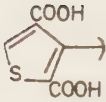
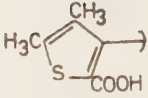
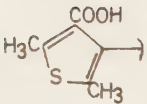
where $R = 1.987 \text{ cal deg}^{-1} \text{ mol}^{-1}$, $k_b = 1.38 \times 10^{-16} \text{ erg deg}^{-1}$ (Boltzmann's constant), $h = 1.104 \times 10^{-28} \text{ erg min}$ (Planck's constant) and $X = 1$ (the transmission coefficient).

Racemization of IX in diglyme indicated that the acidic form is more optically stable than the corresponding tetra-anionic form, as it was necessary to raise the temperature approximately 40°C. It seems that carboxyl groups are more effective blocking groups than carboxylate groups. This has also been observed for 2,2'-dicarboxy-4,4',5,5'-tetramethyl-3,3'-bithienyl.⁵⁴ In the biphenyl system this is not always valid.⁵

Compound XXIX was impossible to racemize even at temperatures up to 190°C in diglyme. Similarly, Adams et al did not succeed in racemizing the methylacrylic acid II ($R = \text{CH}_3$) on refluxing it in absolute ethanol for fifteen hours or in glacial acetic acid for twelve hours.¹⁵

The ¹H NMR spectrum of the menthenyl substituted hexenyne IV and LVII showed doublets due to hindered rotation. The coalescence of the doublet from the vinylic methyl group of LV occurred at 59°C in *o*-dichlorobenzene at 100 MHz, corresponding to a rotational barrier of 18.4±0.3 kcal/mol.

Table 1. Activation parameters^a for the racemization of some optically active bithienylcarboxylic acids

Compound	Solvent	$\Delta H^\ddagger$ (kcal mol ⁻¹)	$\Delta S^\ddagger$ (cal deg ⁻¹ mol ⁻¹)	Ref
	diglyme	21.5 ± 0.1	- 9.4 ± 3.2	
	0.01 N NaOH	24.4 ± 0.1	- 7.4 ± 0.4	
	0.1 N NaOH	26.9 ± 0.4	-13.6 ± 0.9	54
	0.1 N NaOH	22.8 ± 0.8	-13.1 ± 2.2	55

^a The limits of error in this table are standard deviations obtained from least-squares treatments of the corresponding data.

5. CIRCULAR DICHROISM AND UV SPECTRA

The exciton theory and the coupled dipole mechanism try to explain the circular dichroism (CD) of biaryls by predicting two CD bands for each transition, separated by a few nm and of similar and relatively high intensities, but of opposite signs.⁵⁶ Another explanation makes use of a rule similar to the octant rule for the carbonyl chromophore, the two aryl chromophores being mutually perturbed and one regarded as substituent on the other. Similar quadrant rules and other sector rules have been formulated for the aromatic chromophore adjacent to a chiral centre.^{57,58} Compounds with a chiral centre in a side chain and biaryls reveal an important difference: The biaryl molecule should give contributions of the same sign to the CD, whereas compounds with a chiral centre in the side chain give contributions of alternating signs from the various groups, which yields a cancelling effect (Fig. 1).

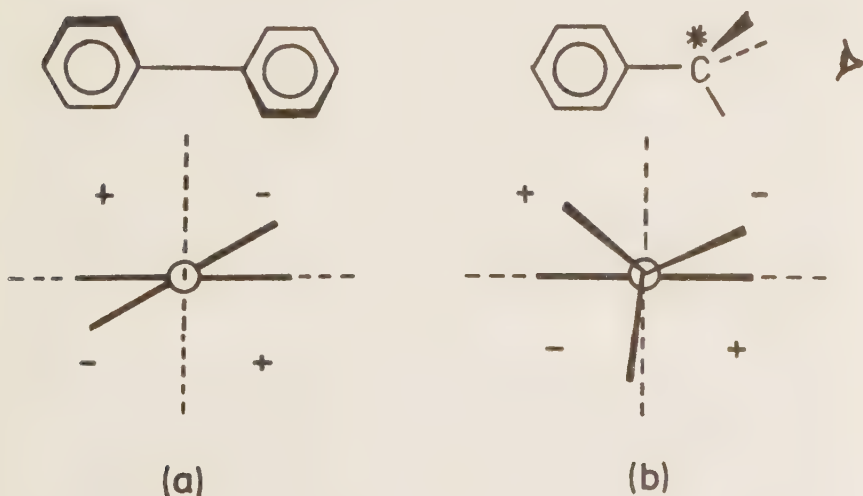


Fig.1

One aim of this investigation was to see if any mutual pattern could be traced in the CD spectra of bithienyls, 3-cyclohexenylthiophenes and thienylacetic acids.

The CD spectra of 3,3'-bithienyls are discussed in Paper (1). In Paper (3) some CD spectra of 3-cyclohexenylthiophenes are discussed and a comparison is made with the CD spectra of some 3,3'-bithienyls. The CD curves of 3-menthene-thiophenes are presented in Paper (4). In Paper (5) CD spectra of some α -methoxy thienylacetic acids are presented and compared with those of 3-cyclohexenylthiophenes.

5.1 CD spectra of some 3,3'-bithienyls

The absolute configurations of 3,3'-bithienyls are reflected in their CD spectra, as in the case of biphenyls.⁹⁻¹² In the 3,3'-bithienyl series, the 2,2'- and the 4,4'-dicarboxylic acids exhibit rather different CD spectra.⁵⁹⁻⁶¹ The CD spectra of the former acids are relatively insensitive to solvent and ionization of the carboxylic groups, in sharp contrast to the spectra of the 4,4'-dicarboxylic acids.

In the CD spectra of most 3,3'-bithienyls of (R)-configuration, a negative band near or above 250 nm followed by a positive band at shorter wavelengths is observed. Both bands appear to be associated with the 250 nm absorption band. However, 3,3'-bithienyl-4,4'-dicarboxylic acids and 3,3'-bithienyl-4-monocarboxylic acids of (R)-configuration in neutral solvents seem to be characterized by a negative effect near 240 nm.^{59,61}

In Paper (1) the CD spectra of a tetracarboxylic acid is discussed. The bands corresponding to the discussion above are situated at 275-285 nm and at 250-255 nm.

The CD spectrum of compound XII (Fig. 2) also reveals a negative band near 240 nm, but it is difficult to decide whether or not this band may be compared with the 240 nm band observed for 3,3'-bithienyls with (R)-configuration, as 2,4,4'-tricarboxy-2'-hydroxymethyl-3,3'-bithienyl has a comparable

band at 225 nm, but also a negative 245 nm band which rather represents the characteristic Cotton effect of 4,4'-dicarboxylic acids.

The CD spectrum of XII and its dimethyl ester in acetonitrile reveal a band exhibiting fine structure at 320-380 nm (Fig. 2). This Cotton effect is most probably associated with the $n \rightarrow \pi^*$ transition of the formyl chromophore. A corresponding band in the same region was observed previously in the CD spectra of α - β -unsaturated carbonyl compounds.^{62,63} In analogy with this, the CD effect associated with the $n \rightarrow \pi^*$ transition of the carboxyl group in the spectra of 3,3'-bithienyldicarboxylic acids should be sought near 240 nm, where it is observed in the spectra of α - β -unsaturated carboxylic acids,⁶³ i.e. at about 250 nm. In this region, however, there are intense CD effects originating from aromatic transitions, making it difficult to distinguish small bands originating from carboxyl groups.

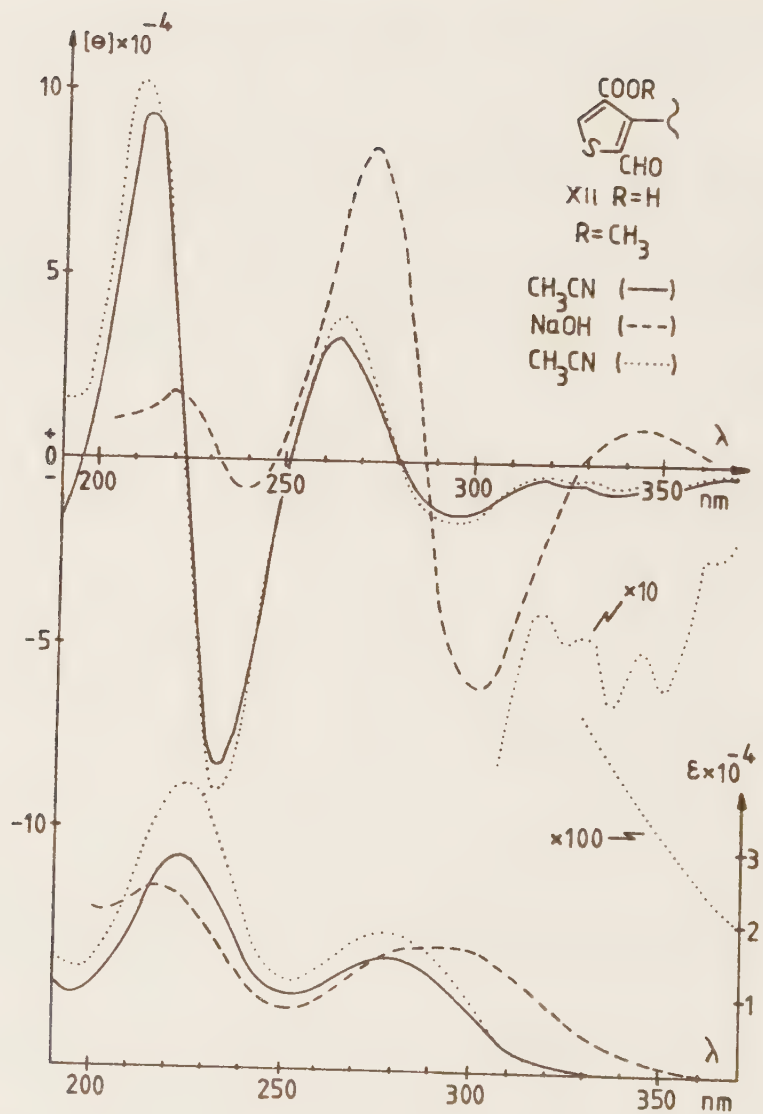


Fig. 2. UV and CD spectra of 4,4'-dicarboxy-2,2'-diformyl-3,3'-bithienyl (XII) in acetonitrile and in 0.01 N sodium hydroxide and of 4,4'-dicarbomethoxy-2,2'-diformyl-3,3'-bithienyl in acetonitrile.

5.2 CD spectra of some cyclohexenylthiophenes

In Fig. 3 the CD spectra of XXIX in acetonitrile, ethanol and 0.01 N NaOH are presented. The spectrum exhibits a negative effect at 250 nm and a positive effect at 200-210 nm. Upon ionization of the acid the negative band is split into two negative bands. The corresponding methyl ester XXX in acetonitrile shows a comparable spectrum. A shoulder at 230 nm on the negative band is however present.

The appearance of the CD spectrum of XXXI (Fig. 7) might be explained by a change in the sign of the previously mentioned 230 nm band from negative in XXIX and XXX to positive in XXXI. It is also possible that a positive band overlaps the broader negative 250 nm band, resulting in the observed 230 nm shoulders in the spectra of XXIX and XXX, and accounting for the very small negative 215 nm band of XXXI.

The carboxyl group in XXIX is reduced to a methyl group in XXXI. It is however not possible to assign any CD band associated with the carboxyl group by comparing the CD spectra of the two compounds. A mesomeric effect of the carboxyl group can be seen on the short wavelength and long wavelength bands.

In Fig. 4 the CD spectrum in acetonitrile of XXIX is compared with that of a monocarboxyl substituted bithienyl and that of the corresponding 3,3'-bithienyl-4,4'-dicarboxylic acid. The three spectra reveals a great resemblance although the bithienyl spectra exhibit somewhat lower intensities.

Compound XXIX may be compared to the styrene chromophore. This chromophore may be considered as formally analogous to a biaryl, in which the aromatic nucleus is replaced by an olefinic double bond.⁶⁴ This view is strongly supported by the similarity of the spectra in Fig. 4. Thus, as far as the vinylthienyl and bithienyl chromophores are concerned, there can hardly be very different mechanisms for the optical activity.

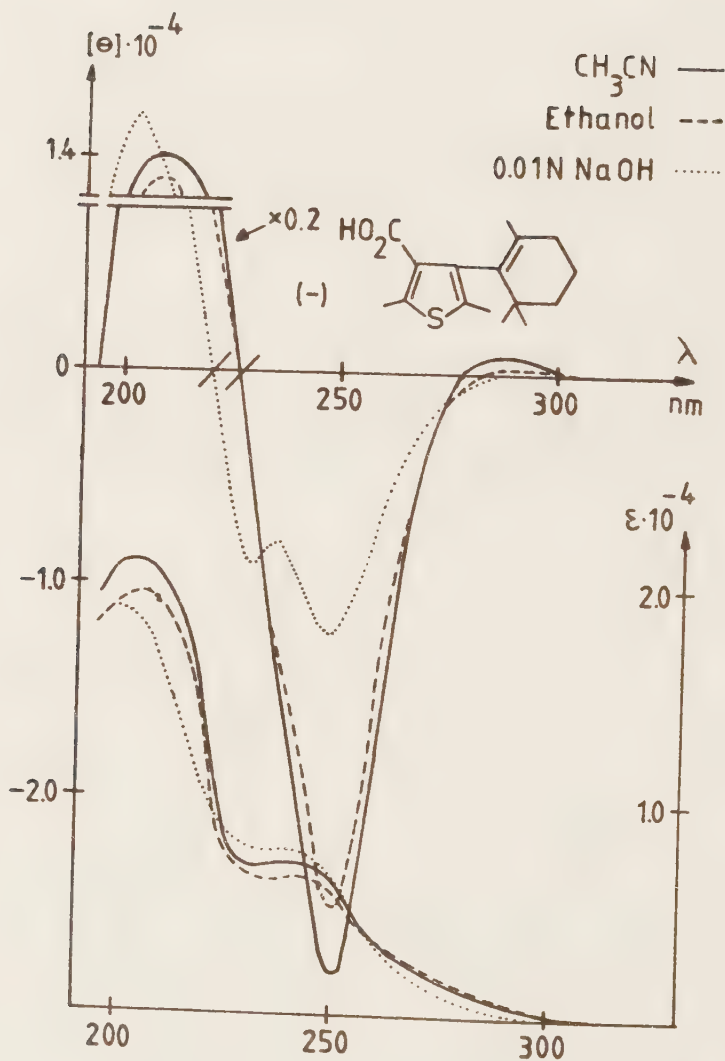


Fig. 3. UV and CD spectra of (-)-2,5-dimethyl-3-(2,2,6-trimethyl-6-cyclohexenyl)-4-thiophenecarboxylic acid (XXIX) in acetonitrile, ethanol and 0.01 N sodium hydroxide.

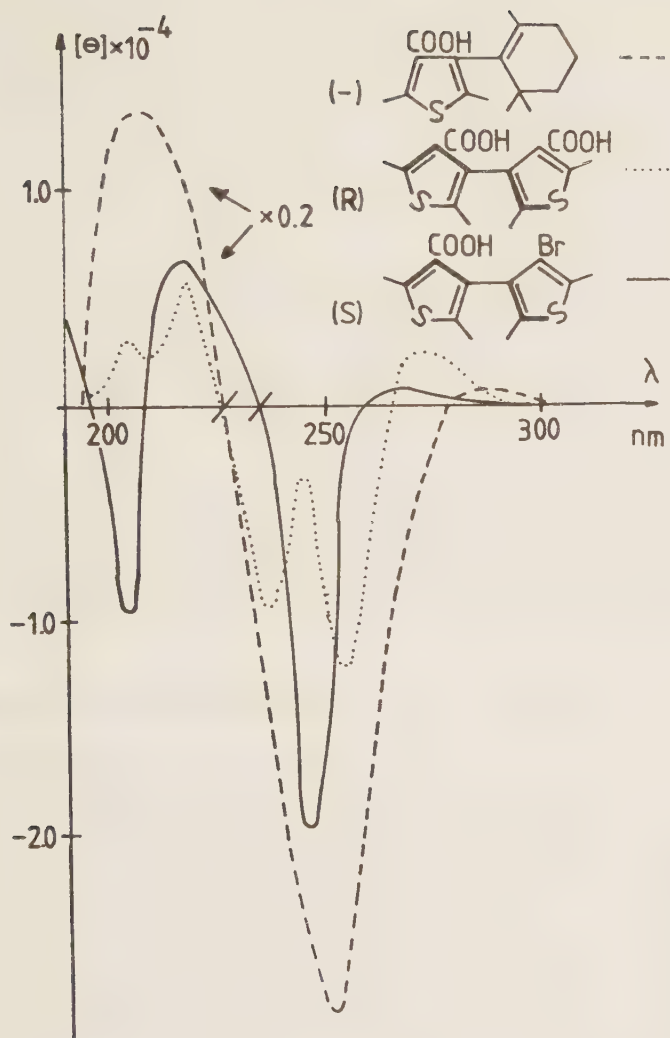


Fig. 4. CD spectra of (-)-2,5-dimethyl-3-(2,2,6-trimethyl-6-cyclohexenyl)-4-thiophenecarboxylic acid (XXIX), (R)-(-)-4,4'-dicarboxy-2,2',5,5'-tetramethyl-3,3'-bithienyl and (S)-(-)-4-bromo-4'-carboxy-2,2',5,5'-tetramethyl-3,3'-bithienyl in acetonitrile.

The styrene chromophore is treated as an inherently dissymmetric system, having a strong dichroism at the 270-280 nm transition. An empirical helicity rule has been proposed; a right-handed chirality of the styrene chromophore is related to a negative Cotton effect at 280 nm, and conversely, a left-handed chirality leads to a positive sign at the same wavelength. This rule was deduced principally from a study of aromatic steroids.⁶⁴

An empirical rule has also been formulated for bithienyls; those of (R)-configuration exhibit a negative 250 nm CD band followed by a positive one at shorter wavelength.³⁰ Bridged compounds of cis-skew conformation corresponding to a left-handed helicity exhibit the same pattern. It is however known that flexible substituents may have a strong influence on the signs of the bands.^{59,61}

The similarities of the spectra in Fig. 4 might indicate a similar helicity of the compounds involved. It is however not possible to determine both configuration and conformation from the CD, and neither is known for compounds XXIX as yet.

5.3 CD and UV spectra of some (-)-menthene substituted thiophenes

In Fig. 5 the CD spectra of compounds XXXVII and XXXIX are shown. They exhibit rather different features compared to the spectra of the cyclohexenyl thiophenes and bithienyls of the (R)-configuration. The 250 nm CD effect is relatively small and positive for the less substituted XXXVII and XXXIX, negative for XL and XLI. The optical activity is derived from the chiral (5R) centre in the menthene ring. In the more substituted compounds, it is also possible that a hindrance of rotation takes place, resulting in a mixture of two epimeric forms. The low intensities of the bands can be explained if compounds XL and XLI are mixtures of diastereoisomers.

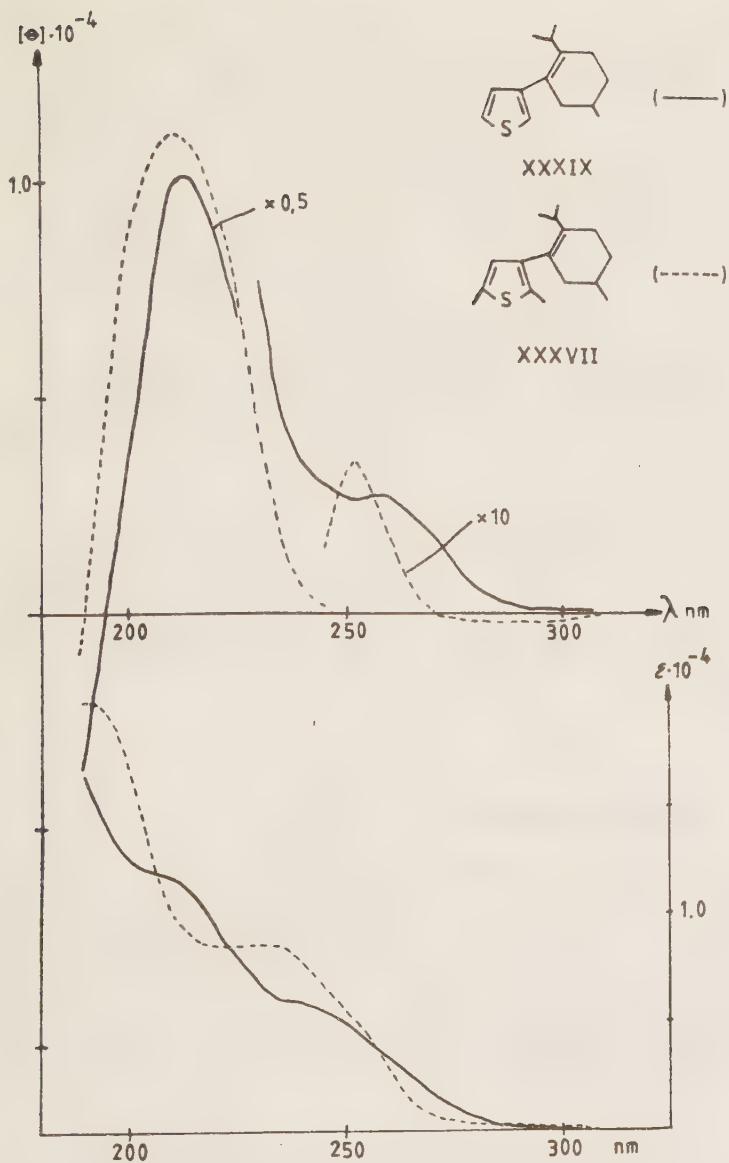


Fig. 5. UV and CD of (+)-3-(1-menthene)thiophene (XXXIX) and (+)-2,5-dimethyl-3-(1-menthene)thiophene (XXXVII) in acetonitrile.

The UV spectra in Fig. 5 reveal an interesting influence of the vinyl groups. In the spectrum of XXXVII, in which the thiophene ring and the vinyl group may be coplanar, an evident UV band at about 210 nm is observed. This "conjugation band" successively diminishes with increasing substitution of the thiophene ring, forcing the vinyl group out of the plane. Another investigation of this effect was made in Paper (6), where the UV spectrum of 3-cyclohexenylthiophene was compared with those of some more substituted derivatives. The effect observed was more pronounced in this case.

The influence of methyl substitution on the conjugation in phenylcyclohexenes has been reported.⁶⁵ It was found that the intensity of the 250 nm UV band decreased with increasing methyl substitution and loss of resonance.

The effect of the carboxyl group of XLI, in which a carbon-oxygen double bond instead of a carbon-carbon double bond may interact, is to shift the short wavelength UV band to longer wavelengths, and to increase the intensity of the band between 250 and 300 nm, eventually in combination with a red shift. Similar behaviour was observed in the spectrum of XXIX (Fig. 4).

5.4 CD of some α -methoxythienylacetic acids

Compounds of the mandelic acid type show high conformational mobility. This prevents the formulation of a general rule. However, in the hydroxy acids certain conformations may be favoured due to stabilization through hydrogen bonds between the hydroxy and carboxyl groups. In the corresponding methoxy acids this is not possible, and an alteration of the conformation on O-methylation of a hydroxy acid might be traced in the CD spectra.

The effects of substitution in the thiophene ring are illustrated in Figs. 6-7. Two methyl groups in positions 2 and 5 result in a doubled intensity and a small shift towards longer wavelength. The 200-220 nm band is now divided into two bands with maxima at 205 and 220 nm.

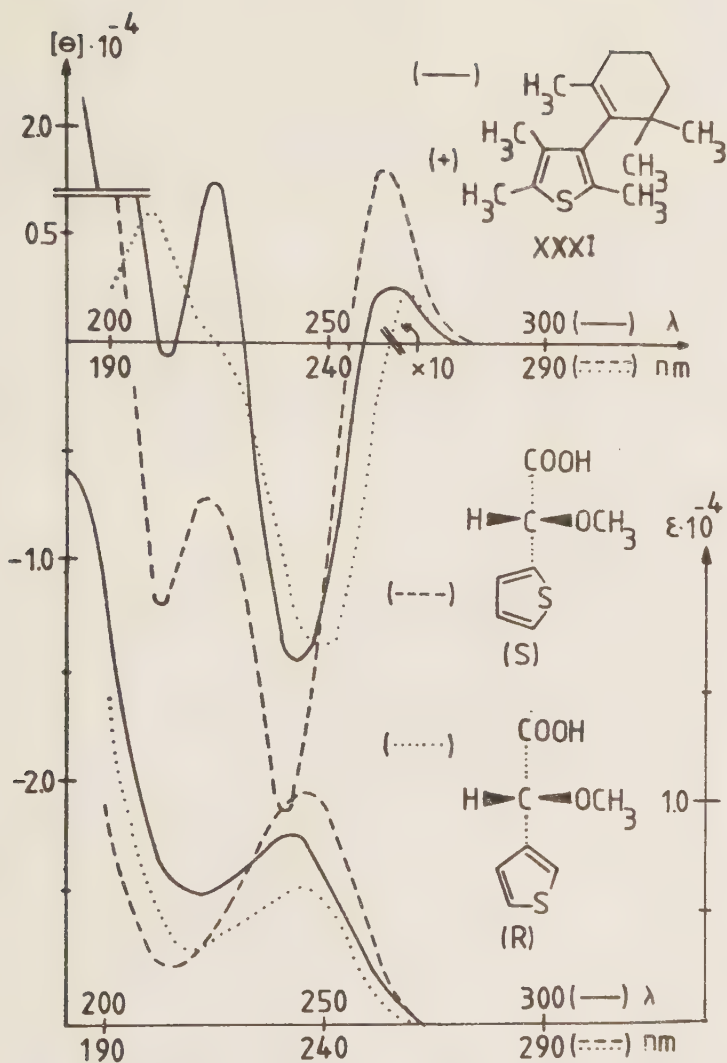


Fig. 6. UV and CD of (+)-3-(2,6,6-trimethylcyclohexen)-2,4,5-trimethylthiophene (XXXI), (S)-(+)- α -methoxy-2-thienylacetic acid and (R)-(+)- α -methoxy-3-thienylacetic acid in acetonitrile.

Exchanging methyl for chlorine causes a small redshift of the 240 nm band. At shorter wavelength the band around 210 nm has reversed sign.

4-Bromo-2,5-dimethyl- α -methoxy thienylacetic acid (XLV) exhibits CD spectra which are rather different from those in Fig. 7. The 240 nm band appears to have decreased considerably in intensity, and the effect of ionization of XLV on the CD is greater than for the other compounds discussed, except for α -methoxy-2-thienylacetic acid.

α -Hydroxy acids are considered to exist in the conformation corresponding to (a) and (b) in Fig. 8, which may be stabilized by hydrogen bonding between the carbonyl group and the hydroxyl group.⁶⁶ Another stable conformation may be that shown in (c) in Fig. 8, which however presupposes an arrangement of the aromatic ring perpendicular to the plane of the carboxyl group for steric reasons.

The substitution of an α -hydroxy group by an α -methoxy group may result in the loss of a stable conformation, which may be reflected in the CD spectra. This was observed in the case of the O-methylation of (S)-atrolactic acid.⁶⁷

In our case, however, the α -hydroxy and the α -methoxy acids exhibit very similar CD spectra. Therefore it can be concluded that the conformational distribution is about the same in the α -hydroxy and α -methoxy acids.

The different spectra of bromo compound XLV might be caused by a change in conformation relative to e.g. XLIII, but it may be difficult to estimate whether this involves a rotation around the C₁-C₂ bond or the C₂-C₃ bond, or both. It is clear that the bromine in the 4-position should have an influence on the freedom of movement of the side chain at the 3-position.

The absolute configurations of XLIII, XLV and XLVII have not been established. However, from the CD spectra it may be deduced by comparison with those of α -methoxy-2-thienylacetic acid, α -methoxy-3-thienylacetic acid and the corresponding hydroxy acids, that the dextrorotatory forms of XLIII and XLVII possess the (S)-configuration. The quite different appearance of the spectrum of XLV makes a decision more

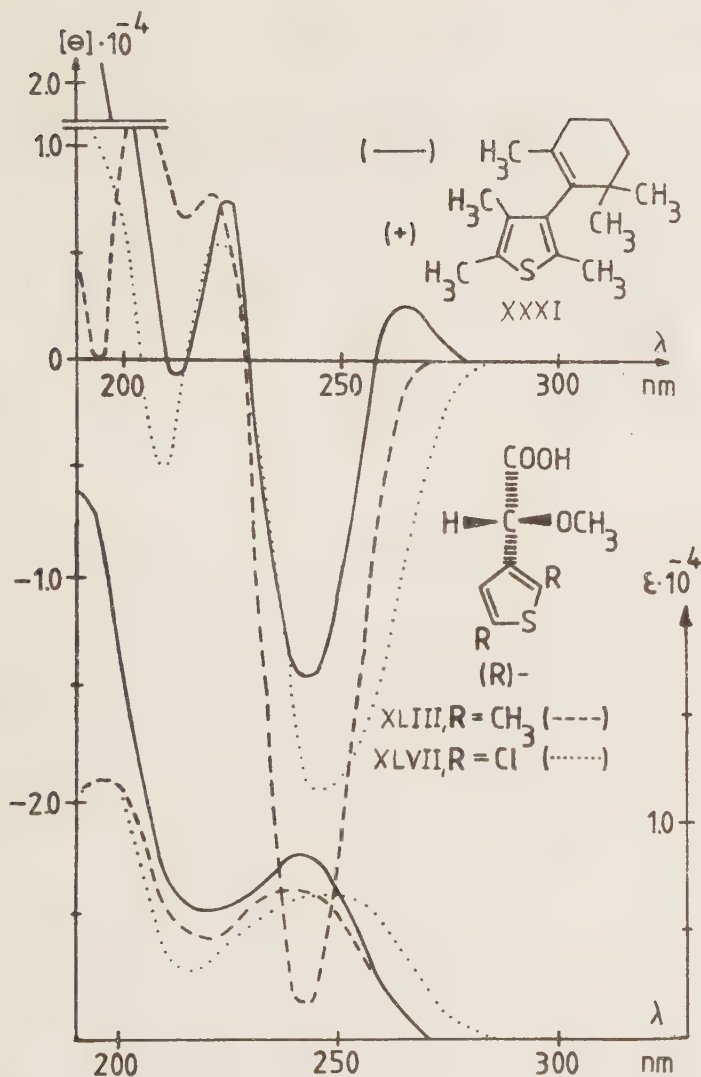


Fig. 7. UV and CD of (+)-3-(2,6,6-trimethylcyclohexen)-2,4,5-trimethylthiophene (XXXI), (+)-2,5-dimethyl- α -methoxy-3-thienylacetic acid (XLIII) and (+)-2,5-dichloro- α -methoxy-3-thienylacetic acid (XLVII) in acetonitrile.

difficult, and it is safer to correlate the configurations of e.g. XLV and XLIII by chemical methods.

One aim of our investigations has been to make comparisons between the CD spectra of thiophene compounds of different types; bithienyls, vinylthiophenes and those with a centre of chirality.

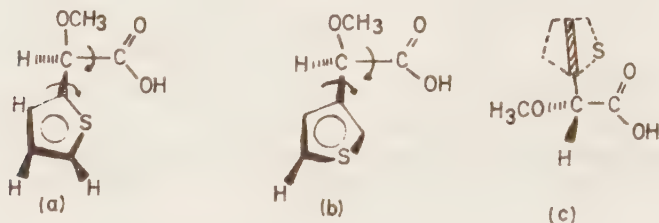


Fig.8

In Fig. 6 the CD of a vinylthiophene, XXXI, is compared with those of some thienylacetic acids. Since the methyl substitution of XXXI causes a red shift, the scale for this compound is shifted 10 nm for better comparison with the thienylacetic acids, and furthermore this comparison has been performed for the enantiomers (S)- α -methoxythienylacetic acid and (R)- α -methoxythienylacetic acid to get the similar relative signs. It may be clearly seen from Fig. 6 that there are great similarities in the spectra. This is valid for the relative signs and positions of the various bands, as well as for the order of magnitudes.

A comparison between the CD spectra of the more similarly substituted 3-thienyl derivatives XXXI, XLIII and XLVII is made in Fig. 7. In this case no wavelength shifts have been made, and although the long wavelength band is missing for XLIII and XLVII, the similarities of the spectra are obvious.

However, before the consequences of these similarities can be formulated in reliable rules for the chiroptical properties of the thienyl chromophore, the absolute configuration and even conformation of the cyclohexenyl derivative XXXI must be deduced.

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